Clinical trial results:
Efficacy and Safety of Two Neoadjuvant Strategies With Bevacizumab in Locally Advanced Resectable Rectal Cancer: A Randomized, Non-Comparative Phase II Study

Summary

EudraCT number	2006-003472-35
Trial protocol	FR
Global end of trial date	23 March 2016

Results information

Result version number	v1 (current)
This version publication date	29 April 2017
First version publication date	29 April 2017

Trial information

Trial identification

Sponsor protocol code	ML19202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00865189
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of two preoperative therapeutic strategies including bevacizumab in participants with newly diagnosed locally advanced rectal cancer.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 91
Worldwide total number of subjects	91
EEA total number of subjects	91

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	62
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 92 participants with resectable rectal cancer were selected and 91 participants were randomized into the study. One participant was not randomized due to non-compliance with the inclusion/exclusion criteria.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)

Arm description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at the fixed dose of 5 milligrams per kilogram (mg/kg) as an IV infusion over 30 to 90 minutes.

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	Leucovorin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Folinic acid was administered at a dose of 200 mg/m^2 as a 2-hour IV infusion.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatine
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was administered at a dose of 85 milligrams per square meter (mg/m^2) as a 2-hour IV infusion.

Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil was administered at a dose of 400 mg/m^2 as an IV bolus, then at a dose of 600 mg/m^2 as a continuous IV infusion for 22 hours in Phase 1, and was administered at a dose of 225 mg/m^2 as a 24-hour IV infusion, 5 days a week, for 5 weeks in Phase 2.

Arm title	Arm B (Bevacizumab, Chemoradiotherapy)

Arm description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

Arm type	Experimental
Investigational medicinal product name	5-fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-fluorouracil was administered at a dose of 400 mg/m^2 as an IV bolus, then at a dose of 600 mg/m^2 as a continuous infusion for 22 hours in Phase 1, and was administered at a dose of 225 mg/m^2 as a 24-hour infusion, 5 days a week, for 5 weeks in Phase 2.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered at the fixed dose of 5 mg/kg as an IV infusion over 30 to 90 minutes.

Number of subjects in period 1	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)
Started	46	45
Completed	34	26
Not completed	12	19
Consent withdrawn by subject	1	-
Death	4	11
Unspecified	1	2
Lost to follow-up	6	6

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)

Reporting group description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

Reporting group title	Arm B (Bevacizumab, Chemoradiotherapy)

Reporting group description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

Reporting group values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)	Total
Number of subjects	46	45	91
Age Categorical			
Units: Subjects			
Adults (18-64 years)	33	29	62
From 65-84 years	13	16	29
Age Continuous			
Units: years			
arithmetic mean	60.38	60.71	
standard deviation	± 8.99	± 9.88	-
Gender Categorical			
Units: Subjects			
Female	15	15	30
Male	31	30	61

End points

End points reporting groups

Reporting group title	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)

Reporting group description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

Reporting group title	Arm B (Bevacizumab, Chemoradiotherapy)

Reporting group description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

Primary: Percentage of Participants With Tumor Sterilization Defined by ypT0-N0

End point title	Percentage of Participants With Tumor Sterilization Defined by ypT0-N0[1]

End point description:

Tumor sterilization was defined as the absence of residual tumor cells in the resected specimen including lymph nodes (ypT0-N0). The rate of sterilization of the tumoral specimen was assessed after surgery on the surgical specimen by local review. Analyses were performed for participants who have been operated as defined by the protocol (within the study and TME technique) and for all participants who have been operated. Reported is the percentage of participants with tumor sterilization. Intent to treat (ITT) population included all the randomized participants who received at least one dose of treatment. Here, number of participants analyzed = participants who were evaluable for this outcome.

End point type	Primary

End point timeframe:

After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not reported due to a limitation of EudraCT application as the application does not allow the capture of a statistical analysis performed within a group.

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	44		
Units: percentage of participants				
number (confidence interval 95%)	23.8 (12.1 to 39.5)	11.4 (3.8 to 24.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Tumor Down-Staging (ypT0-pT2)

End point title	Percentage of Participants With Tumor Down-Staging (ypT0-pT2)

End point description:

A participant with a downstaging was defined as a participant with T3 (T describes the size of the original [primary] tumor) at inclusion and T2 or T1 or T0 after surgery, or with N+ (N describes lymph nodes involvement) at inclusion and N- after surgery and if T is equal at inclusion and after surgery. The clinical tumor-node-metastasis (cTNM) classification was used at inclusion and the pathological staging tumor and nodes (ypTN) classification after surgery. Reported is the percentage of participants with tumor downstaging of the surgical specimen according to the local review and centralized review. ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome. "n" = participants who were evaluable for specified category.

End point type	Secondary

End point timeframe:

After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment)

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	44		
Units: percentage of participants				
number (confidence interval 95%)				
Downstaging, local review (n=41, 44)	65.9 (51.3 to 80.4)	54.5 (39.8 to 69.3)		
Downstaging, centralized review (n=39, 43)	64.1 (49 to 79.2)	55.8 (41 to 70.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Local and Distant Recurrences

End point title	Percentage of Participants With Local and Distant Recurrences

End point description:

The percentage of participants with a recurrence was described by type of recurrence (local and distant recurrence). ITT population.

End point type	Secondary

End point timeframe:

After surgery (Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment)

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: percentage of participants				
number (confidence interval 95%)				
Participants with a local recurrence	2.2 (0.1 to 11.5)	6.7 (1.4 to 18.3)		
Participants with a distant recurrence	17.4 (7.8 to 31.4)	13.3 (5.1 to 26.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Second Cancer, Local or Regional Recurrence, Distant Metastasis, or Death

End point title	Percentage of Participants With Second Cancer, Local or Regional Recurrence, Distant Metastasis, or Death

End point description:

ITT population.

End point type	Secondary

End point timeframe:

Baseline up to approximately 6 years

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: percentage of participants				
number (not applicable)	30.4	33.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-Free Survival (DFS)

End point title	Disease-Free Survival (DFS)

End point description:

The DFS was defined as the time from the first treatment intake to disease recurrence assessed (second primary cancer, local or distant recurrence, distant metastases) or death from any cause. The DFS was analyzed using Kaplan-Meier method. ITT population. Here, 9999 and 99999 indicates that median and upper limit of 95% CI, respectively, were not reached due to low number of DFS-events.

End point type	Secondary

End point timeframe:

From first time of the treatment administration to the date of second cancer, local or regional recurrence, distant metastasis or death from any cause (up to approximately 6 years)

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: months				
median (confidence interval 95%)	68.3 (68.3 to 99999)	9999 (53 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

End point title	Percentage of Participants Who Died

End point description:

ITT population.

End point type	Secondary

End point timeframe:

Baseline up to approximately 6 years

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		

Units: percentage of participants				
number (not applicable)	8.7	24.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

The overall survival was defined as the time from the first treatment intake to death from any cause. ITT population. Here, 9999, 999 and 99999 indicates that median and 95% CI were not reached due to the low number of deaths.

End point type	Secondary

End point timeframe:

From the first treatment administration to the date of death (up to approximately 6 years)

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: months				
median (confidence interval 95%)	9999 (999 to 99999)	9999 (999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Cycles of Induction Chemotherapy

End point title	Number of Cycles of Induction Chemotherapy[2]

End point description:

ITT population. Only Arm A participants received induction treatment.

End point type	Secondary

End point timeframe:

6 cycles (12 weeks; cycle length = 14 days)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only applicable for Arm A

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: cycles				
arithmetic mean (standard deviation)	5.8 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Cycles of Chemotherapy

End point title	Number of Cycles of Chemotherapy
End point description:	
ITT population.	
End point type	Secondary
End point timeframe:	
Arm A: Week 16 to Week 23; Arm B: Week 1 to Week 7	

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: cycles				
arithmetic mean (standard deviation)	4.4 (± 1.5)	4.8 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Cycles of Radiotherapy

End point title	Number of Cycles of Radiotherapy
End point description:	
ITT population.	
End point type	Secondary
End point timeframe:	
Arm A: Week 16 to Week 23; Arm B: Week 1 to Week 7	

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: cycles				
arithmetic mean (standard deviation)	4.5 (± 1.5)	5 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Surgery

End point title	Percentage of Participants With Surgery

End point description:

The surgery involving a radical rectal excision using the TME technique. ITT population.

End point type	Secondary

End point timeframe:

Arm A: approximately 28-31 weeks after initiation of treatment; Arm B: approximately 13-15 weeks after initiation of treatment

End point values	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	Arm B (Bevacizumab, Chemoradiotherapy)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: percentage of participants				
number (not applicable)	91.3	97.8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to approximately 6 years

Adverse event reporting additional description:

The safety population included all selected participants who received at least one dose of treatment and corresponded to the ITT population.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Arm B (Bevacizumab, Chemoradiotherapy)

Reporting group description:

In this arm, participants received the Phase 2 and Phase 3 treatments only. The phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (IV infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The phase 3 was surgery involving a radical rectal excision using the TME technique.

Reporting group title	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)

Reporting group description:

In this arm, participants underwent 3 phases of treatment. During the Phase 1, participants received induction chemotherapy with 6 two-week cycles of bevacizumab + Folfox-4 (5-FU + oxaliplatin + folinic acid) for 12 weeks followed by a treatment-free interval of 3 to 4 weeks. The Phase 2 consisted of 7 weeks of bevacizumab + chemoradiotherapy (intravenous [IV] infusion of bevacizumab alone, 2 weeks before administration of the first cycle of chemoradiotherapy, then 5 one-week cycles of chemoradiotherapy [5-FU + radiotherapy], with administration of bevacizumab every two weeks [Cycles 1, 3 and 5]) followed by a treatment-free interval of 6 to 8 weeks. The Phase 3 was surgery involving a radical rectal excision using the total mesorectal excision (TME) technique.

Serious adverse events	Arm B (Bevacizumab, Chemoradiotherapy)	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 45 (40.00%)	21 / 46 (45.65%)	
number of deaths (all causes)	11	4	
number of deaths resulting from adverse events			
Vascular disorders			
Phlebitis			
subjects affected / exposed	1 / 45 (2.22%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			

subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 45 (2.22%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal pain			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectoprostatic fistula			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal fistula			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anastomotic fistula			
subjects affected / exposed	4 / 45 (8.89%)	4 / 46 (8.70%)	
occurrences causally related to treatment / all	4 / 4	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	2 / 45 (4.44%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal anastomosis complication			
subjects affected / exposed	0 / 45 (0.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			

subjects affected / exposed	2 / 45 (4.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic complication			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's encephalopathy			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 45 (0.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	2 / 45 (4.44%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 45 (2.22%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 45 (2.22%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Enteritis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 45 (4.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postoperative abscess			
subjects affected / exposed	2 / 45 (4.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pilonidal cyst			
subjects affected / exposed	1 / 45 (2.22%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 45 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 45 (4.44%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Arm B (Bevacizumab, Chemoradiotherapy)	Arm A (Bevacizumab, Induction Chemotherapy, Chemoradiotherapy)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 45 (97.78%)	46 / 46 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 45 (15.56%)	11 / 46 (23.91%)	
occurrences (all)	10	13	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 45 (13.33%)	17 / 46 (36.96%)	
occurrences (all)	7	32	
Mucosal inflammation			

subjects affected / exposed	4 / 45 (8.89%)	7 / 46 (15.22%)	
occurrences (all)	4	8	
Fatigue			
subjects affected / exposed	2 / 45 (4.44%)	4 / 46 (8.70%)	
occurrences (all)	2	9	
Pyrexia			
subjects affected / exposed	0 / 45 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	1 / 45 (2.22%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	2 / 45 (4.44%)	15 / 46 (32.61%)	
occurrences (all)	2	17	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 45 (2.22%)	12 / 46 (26.09%)	
occurrences (all)	1	16	
Blood potassium decreased			
subjects affected / exposed	1 / 45 (2.22%)	5 / 46 (10.87%)	
occurrences (all)	1	6	
Weight decreased			
subjects affected / exposed	2 / 45 (4.44%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
Injury, poisoning and procedural complications			
Anastomotic fistula			
subjects affected / exposed	2 / 45 (4.44%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
Wound dehiscence			
subjects affected / exposed	5 / 45 (11.11%)	2 / 46 (4.35%)	
occurrences (all)	6	2	
Wound complication			

subjects affected / exposed	1 / 45 (2.22%)	4 / 46 (8.70%)	
occurrences (all)	1	4	
Radiation skin injury			
subjects affected / exposed	1 / 45 (2.22%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 45 (0.00%)	22 / 46 (47.83%)	
occurrences (all)	0	30	
Paraesthesia			
subjects affected / exposed	2 / 45 (4.44%)	11 / 46 (23.91%)	
occurrences (all)	2	16	
Headache			
subjects affected / exposed	2 / 45 (4.44%)	7 / 46 (15.22%)	
occurrences (all)	2	8	
Dysaesthesia			
subjects affected / exposed	0 / 45 (0.00%)	4 / 46 (8.70%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	24 / 45 (53.33%)	25 / 46 (54.35%)	
occurrences (all)	28	35	
Proctitis			
subjects affected / exposed	18 / 45 (40.00%)	21 / 46 (45.65%)	
occurrences (all)	19	23	
Nausea			
subjects affected / exposed	7 / 45 (15.56%)	24 / 46 (52.17%)	
occurrences (all)	7	38	
Constipation			
subjects affected / exposed	3 / 45 (6.67%)	15 / 46 (32.61%)	
occurrences (all)	3	16	
Abdominal pain			
subjects affected / exposed	5 / 45 (11.11%)	7 / 46 (15.22%)	
occurrences (all)	5	10	
Rectal haemorrhage			

subjects affected / exposed	2 / 45 (4.44%)	9 / 46 (19.57%)	
occurrences (all)	2	10	
Abdominal pain upper			
subjects affected / exposed	4 / 45 (8.89%)	5 / 46 (10.87%)	
occurrences (all)	4	5	
Anorectal discomfort			
subjects affected / exposed	7 / 45 (15.56%)	1 / 46 (2.17%)	
occurrences (all)	7	1	
Proctalgia			
subjects affected / exposed	3 / 45 (6.67%)	4 / 46 (8.70%)	
occurrences (all)	3	4	
Haemorrhoids			
subjects affected / exposed	2 / 45 (4.44%)	4 / 46 (8.70%)	
occurrences (all)	2	4	
Vomiting			
subjects affected / exposed	0 / 45 (0.00%)	6 / 46 (13.04%)	
occurrences (all)	0	6	
Rectal tenesmus			
subjects affected / exposed	3 / 45 (6.67%)	1 / 46 (2.17%)	
occurrences (all)	3	1	
Stomatitis			
subjects affected / exposed	1 / 45 (2.22%)	3 / 46 (6.52%)	
occurrences (all)	1	3	
Abdominal pain lower			
subjects affected / exposed	3 / 45 (6.67%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Gingivitis			
subjects affected / exposed	0 / 45 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 45 (0.00%)	4 / 46 (8.70%)	
occurrences (all)	0	5	
Alopecia			

subjects affected / exposed	0 / 45 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Pruritus			
subjects affected / exposed	0 / 45 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	13 / 45 (28.89%)	20 / 46 (43.48%)	
occurrences (all)	18	31	
Dysuria			
subjects affected / exposed	10 / 45 (22.22%)	12 / 46 (26.09%)	
occurrences (all)	10	12	
Pollakiuria			
subjects affected / exposed	3 / 45 (6.67%)	2 / 46 (4.35%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 45 (0.00%)	3 / 46 (6.52%)	
occurrences (all)	0	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 45 (8.89%)	2 / 46 (4.35%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 45 (6.67%)	6 / 46 (13.04%)	
occurrences (all)	3	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2007	The following changes were implemented: Minor modifications allowing to clarify some points and adding supplemental information in the inclusion and exclusion criteria, the follow-up of targeted events, the participant's follow-up period in case of emergence of toxicity, modifications in the protocol and the participant's information form for the ancillary study, and update of the list of Investigators.
02 June 2008	This amendment was implemented to update and clarify some exclusion criteria related to study treatments and disease, include the safety data of bevacizumab updated on November 2007. The last updates being incorporate in the protocol and the participant's consent form.
08 September 2015	This amendment was implemented to change the secondary efficacy endpoint "progression-free survival" by "disease-free survival".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported